TODAY'S MEDICAL PROBLEMS IN IONIZING RADIATION*

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BEFORE I begin this discussion of "Today's Medical Problems in Ionizing Radiation", I would like to emphasize that not all the occupational health problems in the Atomic Energy industry are associated with the ionizing radiations. We still have to prevent deaths from such commonplace hazards as carbon tetrachloride, high explosives, and falls from scaffolds. In fact, most of the deaths to date in the United States Atomic Energy Commission program have been from these causes. Further, we have to be concerned about the more subtle industrial hazards, such as beryllium and the possible hazards of the whole gamut of the rare earths which are being used more and more in quantity in modern technological developments.

For most industrial toxins we can relate the cause and effect with considerable confidence. There are certain signs and symptoms, and pathologic changes induced by the individual agents, or groups of agents, such as arsenic, lead, mercury and certain organic solvents which make a characteristic picture. With radiation it has become popular to assume that everything is different, i.e., the effects are totally nonspecific and can be only estimated or assumed on the basis of statistical probability.

I have a feeling that a few large-scale statistical studies of delayed effects from exposure to sublethal levels of many noxious substances would yield disconcertingly positive results of much the same general sort that we associate with the long-term effects of radiation exposure in humans.

The genetic effects of exposure of the gonads to ionizing radiation are an open book for all to read, compared to the mass of ignorance of the genetic effects of most chemicals. Certainly the prompt effects of

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relatively heavy exposure to ionizing radiations, either to the whole body or to local regions of the body, are as readily identifiable as are the effects of gross over-exposure to other toxic agents. Even here there will be the same problems of diagnosis, as evidenced by the Lockport, New York, radar installation exposures which went undiagnosed for 24 hours. I refer here to the syndrome of acute whole body radiation exposure, and to the local erythemas, and the more severe effects seen in heavy irradiation of the skin. It is when we get into the delayed effects, especially genetic effects and the leukemogenic effects of radiation, that we are confronted with a problem. They are nonspecific, and they have long latent periods before becoming manifest.

The first generation of workers with radiation consisted largely of physicists and radiologists and their technical assistants who pioneered the uses of x-rays and radium in scientific laboratories and in medical practice. They were relatively few in number and were, with few exceptions, not associated with industry. Many of these individuals received severe radiation burns, especially of the fingers and hands, clearly the result of over-exposure to radiation, and a few, like Madame Curie who discovered radium, also accumulated appreciable amounts of radium in their bones. Some died of cancer which developed in skin burns. Madame Curie herself died, at the age of 64, of an aplastic anemia.

The radium dial painters were the first victims of radiation as an occupational disease of industry to come to public attention. When Dr. Harrison Martland reported these cases in the middle twenties, there could be no reasonable doubt as to the cause of the anemias and of the bone destruction. The girls had ingested relatively large quantities of radium and mesothorium in the course of their work and radioactivity was easily demonstrated in their tissues. Many of their more fortunate colleagues have been under careful observation for the past fifteen years by scientists supported by the AEC, and it has become clear that no dial worker has developed bone cancer who had less than one microcurie of radium in her skeleton before good hygienic practices were instituted in the industry in the late twenties. The present maximum permissible concentration for radium has been set conservatively at one-tenth of the above value. There has been no evidence of radiation-induced disease resulting from current practices in the radium dial industry. This indicates that radiation properly controlled need not be in any sense of the word an extraordinary industrial hazard.

The radium dial industry and medical and laboratory uses of radium concerned themselves with a relatively few curies of radium.

With the development of our country's nuclear energy industry, first under the Manhattan Engineering District (MED) and later spearheaded by the AEC, it was early recognized that we were going to have to deal with millions of curies of radioactive materials. Dr. Robert Stone, who had been responsible for the radiation health program of the preliminary work at the Radiation Laboratory, Berkeley, and at the University of Chicago, which led to the establishment of the MED, was extremely radiation-health conscious. He not only established a pattern of control of radiation hazards which led to the remarkable health of the atomic bomb project, but also insisted on a strong program of research on the biological effects of radiation, on health physics control, and on related problems.

Dr. Stafford Warren was appointed Medical Director of the MED when it was set up in 1942. As industrial scale activities got under way, he and his colleagues intensified and broadened both the radiation health control activities and the corollary research effort. It can be said in all truthfulness that, except for the remarkably few clear-cut and well-documented accident situations which occurred, there is no evidence that any individual worker under the MED suffered injuries from working with radiation on the project. The same has been true for AEC operations.

The effects of radiation exposure fall logically into three general categories. Prompt effects on the individual exposed, delayed effects on the individual exposed, and genetic effects or effects that might become manifest in future generations.

The prompt effects result from relatively large exposures received over very short periods of time. A few hundred r units received by the skin in a matter of minutes will lead to transient erythema of the skin. A few thousand r units received in a short period of time are followed by what looks like a severe sunburn with vesical formation. Even this latter effect usually heals without further evidence of damage. Higher single doses, several thousand r units, produce loss of the germinal and pigment cells, and healing by scar formation with permanent changes in the blood supply to the damaged area. Years later in such damaged skin, cancer may develop. Repeated exposures in the few hundred rad range, but adding up to several thousands of rads, can also lead to scarring and cancer formation. The same sort of thing can happen in the deeper tissues such as bone. Nevertheless, it is extremely rare for cancer to be induced in bone or other human tissue which has been subjected to a few thousands of rads of radiation in the course of x-ray treatment.

In Japan in 1945, at Hiroshima and Nagasaki, thousands of persons received, in a matter of seconds to minutes, hundreds of rads of radiation to the entire body. Almost all of those receiving more than 600 rads died within a few days or weeks. Of those receiving 400 to 500 rads all became ill and approximately 50 per cent died within a month or two. The symptoms were characteristic of this agent, just as the symptoms known to be associated with acute lead, arsenic, carbon tetrachloride, or mercury poisoning are characteristic. There were initial nausea and vomiting, following in a week or two by loss of hair, small hemorrhages into the skin and other tissues and a dramatic loss of ability to combat common bacterial infections. Death was from overwhelming infection, complicated by hemorrhages from the mucous membranes. Of those persons who received doses of 200 rads or less, some developed similar symptoms but very few died. Probably no one who received less than 100 rads whole body exposure died from the radiation exposure alone.

Those individuals who recovered from these exposures at this very high dose rate show today, with exceptions to be noted later, no evidence of radiation injury. With the exceptions discussed in the following paragraph, they are in generally good health and have had the normal number of healthy children.

These people have been under continuous observation by the Atomic Bomb Casualty Commission,[1] an operating branch of the U.S. National Academy of Sciences-National Research Council and, more recently, in full cooperation with the Japanese Ministry of Welfare. Two delayed effects have been observed. One, there are about one hundred persons with detectable opacities of the lens of the eye. All were within 1,000 meters of the hypocenter of the burst; i.e., they received high exposure to neutrons. To date, only two of these persons have had interference with vision requiring operation. One can conclude from this that clinically important lens opacities were extremely rare even at high-level, almost instantaneous exposures.

The other delayed effect which has been observed is leukemia. Eighty-two of the 15,000 survivors, who were still living in the two cities in 1950 and who had been within 1,500 meters of the hypocenters at the time of the bombings in 1945, have developed leukemia in the twelve years, 1947 through 1958. The leukemia incidence rate in the Japanese population is about three in 100,000 per year. Five or six of the survivors therefore would have developed leukemia anyway. The rest of the cases of leukemia may properly be attributed to the radiation from the atomic bombs. In general, the higher the total dose the more liable have been the survivors to develop leukemia. The incidence rate among those who were within 1,500 meters of the hypocenter of the bomb and who probably received upwards of 100 rads of acute exposure has averaged, for these years, about ten times that seen among the control population.

One other late effect of high level, high dose rate, whole-body radiation exposure should be mentioned. It has not yet been observed in Japan, but has been observed regularly in small mammals. I refer to a decrease in the average life span not accounted for by the increased incidence of leukemia. It amounts to approximately 25 per cent of an exposed group's average life expectancy from the time of irradiation, per LD_{50} exposure. For man, the average shortening of life span would be expected to be of the order of 5 per cent per 100 rads of high level, high dose rate exposure.

One very striking observation seen regularly in experimental animals is that shielding an appreciable part of the body from the radiation, say an entire extremity, arm or leg, not only permits survival at doses which would otherwise be fatal but prevents the production of radiation-induced leukemia later in life. This is important when one bears in mind the fact that under many working conditions the radiation exposure will be far from uniform.

So far I have discussed the effects of exposures to high doses at high dose rates comparable to the effects of taking a lethal or sublethal dose of poison or inhaling a lethal or sublethal amount of carbon monoxide gas. The effects of radiation exposures at very low dose rates, or in very small increments as occur in normal plant operations, or even somewhat above these levels, are in question. Because the number of individuals showing effects under these circumstances would be very small, even in large populations, it is extremely difficult to get statistically meaningful data. For instance, we have no evidence of adverse effects in human beings at such levels of exposure, in spite of the tens of thousands of persons who have worked with radiation over the past 20 years. This may in part be due to the fact that the great majority of workers in Atomic Energy Commission establishments receive well below 30 per cent of the permissible external radiation exposure. More likely it is related to the fact that in experiments to date, at dose rates even considerably higher than permissible for workers, and with total doses of one or two hundred rad, there is no clear evidence of permanent effects such as are apparent from acute exposures at the same total dose. This holds as well for the effect of life span as for cancer or leukemia induction. In general, the effects of radiation, like those of toxic drugs, manifest themselves the sooner the higher the dose and the higher the dose rate. It may well be that at low dose rates, and with total doses of 100 to 200 rad, the latent period for the effect is longer than the life expectancy of the individual exposed. Dr. Henry Kohn of the University of California School of Medicine in San Francisco observed something of this sort when he irradiated rats past middle life with doses and at high dose rates which would have had an appreciable effect on the animals' average life span, if they had been young adults at the time of exposure. There was no curtailment of average life span.

It is with these considerations in mind that the United Nations Scientific Committee on the Effects of Atomic Radiation,[3] in its 1958 report on the possible effects of radioactive fallout, stated that, whereas, in the present state of our knowledge, they could not rule out the possibility of a certain number of cases of leukemia being induced by fallout, there might well be no cases induced. Since then the experimental evidence gives even less support to the idea that leukemia induction and life span effects are strictly proportional to dose, irrespective of dose rate. In fact, in one experiment involving several thousand mice exposed to levels of 200 rad and upward of almost instantaneous atomic bomb radiation, the effect was clearly not strictly proportional to dose. We are still pursuing this problem, but it is hard and expensive work. It will take time and will involve hundreds of thousands of animals to determine, once and for all, whether or not there is a dose or a dose rate below which there is no effect; or to develop the experimental data, at relatively low doses or with continuous exposure at low dose rates, which will permit us to estimate with reasonable confidence what the probability of getting leukemia is for a worker who, under normal working conditions, has accumulated 50 to 150 r units over his occupational life. The experimental data in hand indicate that, if not zero, it will be well below the probability that one or two cases of radiation-induced leukemia would appear in the ensuing twenty years among a thousand workers who had received 100 rads of acute exposure. Of particular interest are Henry Kaplan's[4] brilliant researches on mouse lymphoma in C 57 BL mice. They suggest that proliferation of the virus associated with this form of mouse lymphoma to levels leading to tumor development requires "an adequate reservoir of immature cells" which, except for the neonatal state, is only achieved in response to acute whole body exposure to several hundreds of r of radiation.

It is extremely important to keep in mind in this context that, according to the Federal Radiation Council Report No. 1,[5] the average worker will have been receiving radiation exposure to the bone marrow from natural and from medical sources of between 5 and 9 rads every thirty years. The lungs may have received an additional 4 to 45 rads per thirty-year period from radon gas given off by the earth and the walls of houses. What, if anything, these nonoccupational exposures have to do with the natural incidence of leukemia and lung cancer, is unknown. They can be a very confusing factor when it comes to determining whether or not a given case of leukemia or cancer was the result of occupational exposure to radiation. For instance, the average worker at an AEC establishment, who started working with radiation at the age of 30, will, by the time he is 50, have accumulated well below 20 rads of exposure, but he will have received, depending on circumstances, from 7 to 15 rads exposure to his bone marrow from medical and natural sources, plus 6 to 75 rads of exposure to his lungs.

As to possible genetic effects from radiation, it is quite clear from studies in experimental animals that radiation of the germ cells does induce mutations, and that even relatively small doses will do so. These studies were begun by Dr. Herman Muller at the University of Texas in the 1920's. In 1958, on the recommendation of the National Committee for Radiation Protection (NCRP) and the International Commission on Radiation Protection (ICRP), the basic maximum permissible concentration levels for radiation exposures in AEC plants and laboratories were reduced by a factor of about three; not because of any evidence of injury to workers under the wartime permissible levels, but because radiobiological research had better defined the potential genetic hazards of radiation. Further, there was no overriding reason for not lowering the permissible levels in the interest of keeping at a minimum the average radiation exposure of the population as a whole. This latter, that is, the average exposure of the population as a whole, is the key factor in the genetic effects of radiation, not the amount of exposure any given individual might receive. This is not the place for a detailed discussion of the scientific basis for this point of view, but it may be helpful to mention that a very extensive large study of the genetic effects of the atom bomb radiations in the surviving Japanese population at Hiroshima and Nagasaki was carried out with AEC support through the Atomic Bomb Casualty Commission under the auspices of the National Academy of Sciences.[6] Forty thousand pregnancy terminations were studied. The only statistically significant observation which could be made, and which even today some geneticists question, is that the ratio of girl babies to boy babies born was slightly higher than was observed in the unirradiated control population. The number of abnormal children born to the irradiated parents was not significantly different statistically from the number born to nonirradiated parents. This is because more than 95 per cent of the mutations are lethal, most of which are lethal early in gestation, relatively few manifesting themselves in a readily identifiable manner after birth.

As to the effects of high dose rate as compared with relatively low dose rate exposures from the standpoint of genetic effects, enough has been done to establish pretty well that, whereas almost any amount of radiation exposure, however small, may have some genetic effect, there is a difference between the effects at high dose rates, as opposed to lower dose rates, of a factor of about four. Within each of the dose rate ranges, however, the effect appears to be proportional to dose, though no studies have yet been possible at dose rates as low as would be encountered in normal industrial activities.

What about the manner of exposure to radiation in occupational situations? It should be clear from the record that the great majority work in situations where with good radiation hygiene practices the chances of over-exposure are minimal. This holds for the radium industry where, since the late twenties, accumulation of high levels of radium in bone has not occurred. It is true of AEC operations where the vast majority of workers receive well below one third the permissible levels of exposure. With equally routine precautions, this situation could carry over to the uses of x-rays and radium in medical practice.

Most of the significant exposures in AEC operations have been in rather specialized situations and have involved relatively few persons.

Let us look at some of these.

Criticality accidents are the most dramatic. There have been a number of accidental criticality excursions in AEC operations, but only six in which overexposures to personnel have occurred. There have been at the Los Alamos Scientific Laboratory three such accidents involving a total of about 12 persons and with three fatalities. The Oak Ridge National Laboratory accident in 1958 involved five persons. There were no fatalities. The Argonne National Laboratory accident in 1952 involved four persons. There were no fatalities. The SL-1 accident at the National Reactor testing station resulted in the death of three persons, and we are not yet certain as to the exact cause. It is certain, however, that there was an explosive force involved and that a nuclear excursion did occur.

We have the day-to-day problem of protecting workers from the inhalation of plutonium and other radionucleids in plant operations. This often requires elaborate and costly precautions. Activities of scientists, construction workers, and others at weapons-test sites involve potential overexposures. Considering the numbers of persons involved and the amount of radioactivity produced, overexposures have been relatively few.

In chemical processing operations the routine control is a major enterprise. Actually in this activity the biggest hazards occur from clean-up operations after spills in hot cells. In one instance at the Oak Ridge National Laboratories (ORNL) there was an explosion which involved plutonium, and though no one accumulated more than 2 per cent of the permissible body burden for plutonium, it was of interest that most of what was picked up was the result of participation in the clean-up job, not the result of the accident itself.

Of perhaps the greatest concern today to the public is the matter of increasing exposure of the public at large to radiation. Atomic energy activities have made their contribution to this exposure, though it has not been large compared to exposure from natural sources, or when compared to exposure from medical x-rays.

In AEC establishments the principal sources of exposure to the public at large have been from stock effluents, from chemical reprocessing plants, and from reactors: from reactor coolant water returned to streams and rivers. We have had problems with both of these, but the record is, by and large, good over the years. Exposures from these sources, even to persons living in the immediate vicinity of the operations, have been well below the permissible. They have not produced nation-wide increases in exposure. Waste disposal operations have been carefully policed, and I am aware of any but the most minor sort of exposures to the public from this source.

The matter of hazard to the public from the transportation of radioactive materials is one which has given much concern. The AEC has worked in very close cooperation with the Interstate Commerce Commission to keep the likelihood of this kind of accidental exposures to the public minimal. So far there have been no important exposures to even a few people from this source.

Similarly, there is the constant problem of the use of radioisotopes and radiation sources in industry, in universities and in hospitals and scientific laboratories. There have been instances in which nonradiation workers have received more than the permissible exposure, but to date they have been few.

Our biggest problem has been weapons-test activities as sources of local and world-wide exposures. We, of course, have not been the only producers of world-wide fallout. Nevertheless, to date, exposures to the United States population from United States, USSR, United Kingdom, and French weapons tests have been below the guides set forth by the Federal Radiation Council as applicable to normal peacetime activities. There has been a very limited number of persons in the vicinity of the Nevada Test site who received external radiation exposures of 1 to 6 rads, and two persons have accumulated total doses estimated at 10.5 and 13.5 rads. There are also the Rongelap people in the Marshall Islands who were accidentally exposed to heavy fallout on March 1, 1954 and received external whole body exposures of 75 to 175 rads, plus some internal contamination.

To complete the picture I should mention once again the medical and industrial uses of x-rays and radium as sources of radiation exposure. I hope this discussion, with the definitive statements to come by the able speakers who will follow me, will help put the medical aspects of today's problems with the ionizing radiation in good perspective.

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MODERATOR CHADWICK: Dr. Dunham has mentioned the Federal Radiation Council, and also the uncertainty as to whether low doses of radiation produce any effects. This uncertainty prompts the question: How do you establish health policy? In other words, what do you do about a situation in which you cannot be sure whether there are effects or not? In considering this problem, the Federal Radiation Council decided that, in setting health protective standards, it would be prudent to appraise the situation in the most conservative light, from the health point of view. Therefore, the Council concluded that, until evidence to the contrary is available, we should assume that there will indeed be effects from low doses and dose rates.

Consequently, if one accepts that assumption, the setting of health policy—or radiation protection standards, since these are in effect what health policy amounts to—is a matter of deciding how much of a risk society should be asked to accept from radiation in order to enjoy the benefits from applications of radiation. So, we have come to this current cliché of "balancing benefit and risk". Obviously, this is a good deal easier to say than it is to do.

For a moment, let us hark back to something else that Dr. Dunham said. He pointed out that it was his guess that the radiation problem is fundamentally not different from many other problems. And in this particular regard, the balancing of benefit and risk is nothing new to physicians. It is difficult for me to think of medical procedures that do not involve some degree of risk, even the ones that are presumably quite innocuous. Wasn't it the President of the American College of Surgeons who said there was no such thing as minor surgery, only minor surgeons? The point is, physicians have constantly been faced with this matter of deciding to accept some risk from a particular therapeutic, or even in some cases diagnostic procedure, in order to derive some particular benefit, i.e., saving a patient's life, or making an accurate diagnosis in some obscure condition.

So this matter of balancing benefit and risk, while it may sound somewhat formidable—and in fact is, I guess, when you institutionalize it—actually has been going on for a long time. As we consider the various sources of radiation that we are examining this evening, I think we should keep in mind that each of them, except those over which we have no control, is a risk that we are accepting in order to get back to something of value. Hopefully, the decision as to how much risk we are accepting is being made wisely. Let us turn to Dr. Eisenbud, who will give us a sort of broad-brush treatment of the sources of ionizing radiation exposure of the general public.